STIMULATION FOR TREATING EAR PATHOLOGIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from US Provisional Patent Application 60/426,181, filed November 14, 2002, entitled, "Stimulation for treating ear pathologies," which is assigned to the assignee of the present patent application and is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to medical procedures and electrical devices. More specifically, the invention relates to the use of electrical, chemical, mechanical and/or odorant stimulation for treating ear pathologies.

BACKGROUND OF THE INVENTION

The blood-brain barrier (BBB) is a unique feature of the central nervous system (CNS) which isolates the brain from the systemic blood circulation. To maintain the homeostasis of the CNS, the BBB prevents access to the brain of many substances circulating in the blood.

The BBB is formed by a complex cellular system of endothelial cells, astroglia, pericytes, perivascular macrophages, and a basal lamina. Compared to other tissues, brain endothelia have the most intimate cell-to-cell connections: endothelial cells adhere strongly to each other, forming structures specific to the CNS called "tight junctions" or zonula occludens. They involve two opposing plasma membranes which form a membrane fusion with cytoplasmic densities on either side. These tight junctions prevent cell migration or cell movement between endothelial cells. A continuous uniform basement membrane surrounds the brain capillaries. This basal lamina encloses contractile cells called pericytes, which form an intermittent layer and probably play some role in phagocytosis activity and defense if the BBB is breached. Astrocytic end feet, which cover the brain capillaries, build a continuous sleeve and maintain the integrity of the BBB by the synthesis and secretion of soluble growth factors (e.g., gamma-glutamyl transpeptidase) essential for the endothelial cells to develop their BBB characteristics.

PCT Patent Publication WO 01/85094 to Shalev and Gross, which is assigned to the assignee of the present patent application and is incorporated herein by reference, describes apparatus for modifying a property of a brain of a patient, including electrodes applied to a sphenopalatine ganglion (SPG) or a neural tract originating in or leading to the SPG. A control unit drives the electrodes to apply a current capable of inducing (a) an increase in permeability of a blood-brain barrier (BBB) of the patient, (b) a change in cerebral blood flow of the patient, and/or (c) an inhibition of parasympathetic activity of the SPG.

US Patent 5,756,071 to Mattern et al., which is incorporated herein by reference, describes a method for nasally administering aerosols of therapeutic agents to enhance penetration of the blood brain barrier. The patent describes a metering spray designed for per nasal application, the spray containing at least one sex hormone or at least one metabolic precursor of a sex hormone or at least one derivative of a sex hormone or combinations of these, excepting the precursors of testosterone, or at least one biogenic amine, with the exception of catecholamines.

US Patent 5,752,515 to Jolesz et al., which is incorporated herein by reference, describes apparatus for image-guided ultrasound delivery of compounds through the blood-brain barrier. Ultrasound is applied to a site in the brain to effect in the tissues and/or fluids at that location a change detectable by imaging. At least a portion of the brain in the vicinity of the selected location is imaged, e.g., via magnetic resonance imaging, to confirm the location of that change. A compound, e.g., a neuropharmaceutical, in the patient's bloodstream is delivered to the confirmed location by applying ultrasound to effect opening of the blood-brain barrier at that location and, thereby, to induce uptake of the compound there.

PCT Publication WO 01/97905 to Ansarinia, which is incorporated herein by reference, describes a method for the suppression or prevention of various medical conditions, including pain, movement disorders, autonomic disorders, and neuropsychiatric disorders. The method includes positioning an electrode on or proximate to at least one of the patient's SPG, sphenopalatine nerves, or vidian nerves, and activating the electrode to apply an electrical signal to such nerve. In a further embodiment for treating the same conditions, the electrode used is activated to dispense a medication

solution or analgesic to such nerve. The '905 publication also describes surgical techniques for implanting the electrode.

US Patent 6,405,079 to Ansarinia, which is incorporated herein by reference, describes a method for the suppression or prevention of various medical conditions, including pain, movement disorders, autonomic disorders, and neuropsychiatric disorders. The method includes positioning an electrode adjacent to or around a sinus, the dura adjacent a sinus, or falx cerebri, and activating the electrode to apply an electrical signal to the site. In a further embodiment for treating the same conditions, the electrode dispenses a medication solution or analgesic to the site. The '079 patent also describes surgical techniques for implanting the electrode.

The following references, which are incorporated herein by reference, may be useful:

Delepine L, Aubineau P, "Plasma protein extravasation induced in the rat dura mater by stimulation of the parasympathetic sphenopalatine ganglion," Experimental Neurology, 147, 389-400 (1997)

Hara H, Zhang QJ, Kuroyanagi T, Kobayashi S, "Parasympathetic cerebrovascular innervation: An anterograde tracing from the sphenopalatine ganglion in the rat," Neurosurgery, 32, 822-827 (1993)

Jolliet-Riant P, Tillement JP, "Drug transfer across the blood-brain barrier and improvement of brain delivery," Fundam. Clin. Pharmacol., 13, 16-25 (1999)

Kroll RA, Neuwelt EA, "Outwitting the blood brain barrier for therapeutic purposes: Osmotic opening and other means," Neurosurgery, 42, 1083-1100 (1998)

Sanders M, Zuurmond WW, "Efficacy of sphenopalatine ganglion blockade in 66 patients suffering from cluster headache: A 12-70 month follow-up evaluation," Journal of Neurosurgery, 87, 876-880 (1997)

Syelaz J, Hara H, Pinard E, Mraovitch S, MacKenzie ET, Edvinsson L, "Effects of stimulation of the sphenopalatine ganglion on cortical blood flow in the rat," Journal of Cerebral Blood Flow and Metabolism," 8, 875-878 (1988)

Van de Waterbeemd H, Camenisch G, Folkers G, Chretien JR, Raevsky OA, "Estimation of blood brain barrier crossing of drugs using molecular size and shape and h bonding descriptors," Journal of Drug Targeting," 6, 151-165, (1998)

Suzuki N, Hardebo JE, Kahrstrom J, Owman C, "Selective electrical stimulation of postganglionic cerebrovascular parasympathetic nerve fibers originating from the sphenopalatine ganglion enhances cortical blood flow in the rat," Journal of Cerebral Blood Flow and Metabolism, 10, 383-391 (1990)

Suzuki N, Hardebo JE, Kahrstrom J, Owman CH, "Effect on cortical blood flow of electrical stimulation of trigeminal cerebrovascular nerve fibres in the rat," Acta Physiol. Scand., 138, 307-315 (1990)

Major A, Silver W, "Odorants presented to the rat nasal cavity increase cortical blood flow," Chem. Senses, 24, 665-669 (1999)

Fusco BM, Fiore G, Gallo F, Martelletti P, Giacovazzo M, "'Capsaicin-sensitive' sensory neurons in cluster headache: pathophysiological aspects and therapeutic indications," Headache, 34, 132-137 (1994)

Lambert GA, Bogduk N, Goadsby PJ, Duckworth JW, Lance JW, "Decreased carotid arterial resistance in cats in response to trigeminal stimulation," Journal of Neurosurgery, 61, 307-315 (1984)

Silver WL, "Neural and pharmacological basis for nasal irritation," in Tucker WG, Leaderer BP, Mølhave L, Cain WS (eds), Sources of Indoor Air Contaminants, Ann. NY Acad. Sci., 641, 152-163 (1992)

Silver W, "Chemesthesis: the burning questions," ChemoSense, Vol. 2, 1-2 (1999)

Devoghel JC, "Cluster headache and sphenopalatine block," Acta Anaesthesiol Belg., 32(1):101-7 (1981)

The following is a description of a number of medical conditions.

Meniere's disease (endolymphatic hydrops)

Meniere's disease is characterized by acute, spontaneous attacks of spinning vertigo accompanied by ringing and pressure in a particular ear, with temporary decrease in hearing. Symptoms clear between attacks, but in the late stages (months to years of attacks) the hearing loss becomes permanent. Additionally, the other ear may become involved later in the progression of the disease. The mechanism of the disease is swelling of the inner compartment (endolymphatic) of the inner ear. The cause of the disease is unknown, although it is believed that there may be many causes (e.g., trauma, viral

infection, immune-mediated). Current treatment includes modification of diet (avoiding salt and caffeine), medication (diuretics), and surgery (endolymphatic shunt). New treatments under investigation include transtympanic medication (Corticosteroid, Gentamicin, Streptomycin).

Acoustic neurinoma and neuroma

Acoustic neurinoma (acoustic schwannoma) and acoustic neuroma are benign tumors of the vestibular portion and acoustic portion, respectively, of the eighth cranial nerve (the vestibulocochlear nerve).

Post-traumatic vertigo (inner ear concussion)

Symptoms of post-traumatic vertigo (inner ear concussion) include constant lightheadedness, imbalance, and short-term memory loss, occurring sometime after minor head trauma (or severe shaking such as whiplash). The condition may take weeks or months to develop after the trauma.

It is believed that the mechanism of the condition is likely a derangement of an otolith organ (gravity sensor), causing the organ to be receptive to pressure changes and sound within the body or in the environment. This uncontrollable and constant abnormal input into the brain causes a disruption of balance function, and in many cases, a secondary cognitive dysfunction. The delayed onset and response to corticosteroids suggests an autoimmune factor. The condition is caused by a concussion (severe shaking) of the inner ear, probably followed later by an inflammatory response. A leak from the inner ear (perilymph fistula) may interfere with recovery.

The condition is currently treated with surgical closure of fistula, if present. Transtympanic medication, to correct the inflammation and/or decrease the abnormal sensitivity, is also used.

Vestibular neuronitis (acute labyrinthitis)

Vestibular neuronitis (acute labyrinthitis) is characterized by the acute onset, often following a flu-like illness, of severe spinning vertigo. There is no hearing loss or tinnitus. Recovery typically occurs gradually over a period of days to weeks. The mechanism of the condition is typically an inflammation of a vestibular nerve, the nerve that serves the balance mechanism in the inner ear.

Current treatment of the condition includes anti-nausea medications (e.g., Meclizine, Valium) for control of symptoms in the acute phase only. After that, such medications may interfere with compensation and recovery. A short course of corticosteroid and anti-viral medication is also often prescribed.

Autoimmune inner ear disease (AIED)

Symptoms of AIED include reduction of hearing accompanied by tinnitus (ringing, hissing, roaring) which occurs over a few months. Variants are bilateral attacks of hearing loss and tinnitus which resemble Meniere's disease, and attacks of dizziness accompanied by abnormal blood tests for self-antibodies. About 50% of patients with AIED have balance symptoms.

It is generally believed that the mechanism of the condition is related to either antibodies or immune cells that cause damage to the inner ear.

There are currently several protocols for treatment of AIED. In cases with a classic rapidly progressive bilateral hearing impairment, a trial of steroids (Prednisone or Decadron) for 4 weeks may be conducted. For patients that respond positively to the steroids, in most cases a chemotherapeutic medication (e.g., Cytoxan or Methotrexate) will be used over the long term. It has also recently been reported that plasmapheresis may be beneficial. Etanercept (Enbrel) is also emerging as a promising agent for treatment of AIED. Enbrel is an anti-TNF (tumor necrosis factor) drug, given as an injection twice per week. TNF is an inflammatory cytokine.

Dizziness

Dizziness is a subjective sensation of a person's disorientation to his environment. It can take the form of lightheadedness or faint feeling, staggering or falling, or a feeling of movement or spinning. The sensation of spinning in any form or variation is called vertigo. True vertigo is almost always related to ear pathology most commonly due to a disorder of the inner ear, the nerves connecting the ear to the brain, or the part of the brain concerned with balance. Hearing loss, fullness in the ears and tinnitus (noises in the ears) may or may not be present.

The mechanism of dizziness is inflammation or neuritis of the inner ear, disturbance of circulation to the inner ear, fluid buildup in the inner ear, and/or tumors of the inner ear. Treatments for dizziness include antivertigo medication, removal of wax

from the ears, antibiotics and decongestants when necessary, vasodilators to stimulate circulation of the inner ear, medication to reduce inner ear fluid buildup, and surgical treatment of chronic middle ear disease or tumors of the inner ear.

Sudden sensorineural hearing loss (SSHL)

SSHL, or sudden deafness, is a rapid loss of hearing. SSHL can happen to a person instantly or over a period of up to three days. Although there are more than 100 possible causes of sudden deafness, it is rare for a specific cause to be precisely identified. Only 10 to 15 percent of patients with SSHL know what caused their loss. Normally, diagnosis is based on the patient's medical history. Possible causes include the following:

- Infectious diseases;
- Trauma, such as a head injury;
- Abnormal tissue growth;
- Immunologic diseases such as Cogan's syndrome;
- Toxic causes, such as snake bites;
- Ototoxic drugs (drugs that harm the ear);
- Circulatory problems;
- Neurological causes such as multiple sclerosis; and
- Relation to disorders such as Meniere's disease;

Several treatments are used for SSHL, but researchers are not yet certain which is the best for any one cause. If a specific cause is identified, a doctor may prescribe antibiotics for the patient. Alternatively or additionally, a doctor may advise a patient to stop taking any medicine that can irritate or damage the ear. The most common therapy for SSHL, especially in cases with an unknown cause, is treatment with steroids. A diet low in salt is sometimes recommended for patients who also suffer from Meniere's disease.

Two factors that help hearing function properly are good air and blood flow inside the ear. Some researchers believe that SSHL occurs when important parts of the inner ear do not receive enough oxygen. A common treatment for this possible cause is inhalation

of carbogen (a mixture of oxygen and carbon dioxide), which appears to improve air and blood flow inside the ear.

Hearing loss – restorative treatment using neurotrophic factors

US Patent 5,929,041 to Magal, which is incorporated herein by reference, describes methods for preventing and/or treating injury or degeneration of cochlear (and vestibular) hair cells and spiral ganglion neurons (as well as vestibular neurons -- Scarpa's neurons) by administering glial cell line-derived neurotrophic factor (GDNF). The disclosure describes more specifically methods for treating sensorineural hearing loss and vestibular disorders.

The '041 patent describes several causes of hearing loss, including those described in the following citation from the patent. All references cited in the following citation are incorporated herein by reference.

> A variety of commonly used drugs have ototoxic properties. The best known are the aminoglycoside antibiotics, loop diuretics, salicylates and antineoplastic agents such as cisplatin. Ototoxicity has also been described during oral or parenteral administration of erythromycin.
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> Most ototoxic substances cause hearing loss by damaging the cochlea, particularly the auditory hair cells and the stria vascularis, a specialized epithelial organ within the inner ear, that is responsible for the homeostasis of fluids and electrolytes. Secondary neural degeneration may occur many years after an ototoxic event affecting the hair cells. There is evidence that some ototoxic substances may be selectively concentrated within the inner ear, resulting in progressive sensorineural loss despite the discontinuation of systemic administration.
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> A variety of tumors, both primary and metastatic, can produce either a conductive hearing loss, or a sensorineural hearing loss, by invading the inner ear or auditory nerve. A variety of degenerative disorders of unknown cause can produce sensorineural hearing loss. Meniere's syndrome, characterized by fluctuating sensorineural hearing loss, episodic vertigo, and tinnitus, appears to be caused by a disorder of fluid homeostasis within the inner ear, although the pathogenesis remains

unknown. Sudden idiopathic sensorineural hearing loss, causing moderate-to-severe sensorineural deafness, may be due to various causes, including inner ear ischemia and viral labyrinthitis.

Presbycusis, the hearing loss associated with aging, affects more than one third of persons over the age of 75 years. The most common histopathological correlate of presbycusis is the loss of neuroepithelial (hair) cells, neurons, and the stria vascularis of the peripheral auditory system. Presbycusis is best understood as resulting from the cumulative effects of several noxious influences during life, including noise trauma, ototoxicity and genetically influenced degeneration.

Certain neurotrophic factors have been shown to regulate neuronal differentiation and survival during development (Korsching S. J. Neurosci. 13:2739-2748,1993) and to protect neurons from injury and toxins in adult (Hefti, Neurosci. 6:2155-2162, 1986; Apfel et al., Ann Neurol 29:87-89, 1991; Hyman et al., Nature 350:230-233, 1991; Knusel et al., J. Neurosci. 12:4391-4402, 1992; Yan et al., Nature, 360:753-755, 1992; Koliatsos et al., Neuron, 10:359-367, 1993). In situ hybridization studies indicate that mRNAs for the neurotrophin receptors TrkB and TrkC are expressed by developing cochleovestibular ganglia (Ylikoski et al., Hear. Res. 65:69-78 1993; Schecterson et al., Hearing Res. 73: 92-100 1994) and that mRNAs for BDNF and NT-3 are found in the inner ear, including the organ of Corti (Pirvola et al., Proc. Natl. Acad. Sci. USA 89: 9915-9919, 1992; Schecterson et al., Hearing Res. 73: 92-100 1994; Wheeler et al., Hearing Res. 73: 46-56, 1994). The physiological role of BDNF and NT-3 in the development of the vestibular and auditory systems was investigated in mice that carry a deleted BDNF and /or NT-3 gene (Ernfors et al., Neuron 14: 1153-1164 1995). In the cochlea, BDNF mutants lost type-2 spiral neurons, causing an absence of outer hair cell innervation. NT-3 mutants showed a paucity of afferents and lost 87 percent of spiral neurons, presumably corresponding to type-1 neurons, which innervate inner hair cells. Double mutants had an additive loss, lacking all vestibular and spiral neurons. The requirement of TrkB and TrkC receptors for the survival of specific neuronal populations and the

maintenance of target innervation in the peripheral sensory system of the inner ear was demonstrated by studying mice carrying a germline mutation in the tyrosine kinase catalytic domain of these genes (Schimmang et al., Development, 121: 3381-3391 1995). Gao et al. (J. Neurosci. 15: 5079-5087, 1995) showed survival-promoting potency of NT-4/5, BDNF and NT-3 for rat postnatal spiral ganglion neurons in dissociated cultures and that NT-4/5 protected these neurons from neurotoxic effects of the anti-cancer drug cisplatin. Also, BDNF and NT-3 have been shown to support the survival of adult rat auditory neurons in dissociated cultures (Lefebvre et al., NeuroReport 5: 865-868, 1994).

SUMMARY OF THE INVENTION

It is an object of some aspects of the present invention to provide improved methods and apparatus for treating conditions of the ear. Unless usage indicates otherwise, in the context of the present patent application and in the claims, the word "ear" is meant to include the middle ear, internal ear, vestibulocochlear nerve (comprising the vestibular nerve and the auditory nerve) and branches thereof, the cochlea, the semicircular canals, the utricle, and the saccule.

It is an additional object of some aspects of the present invention to provide improved methods and apparatus for delivery of compounds to the ear.

It is yet an additional object of some aspects of the present invention to provide improved methods and apparatus for delivery of compounds to the ear through the blood brain barrier (BBB).

It is still an additional object of some aspects of the present invention to provide improved methods and apparatus for treating ear conditions by increasing blood flow to the ear.

It is also an additional object of some aspects of the present invention to provide improved methods and apparatus for treating ear conditions by increasing the clearance of fluid and/or molecules (e.g., metabolites) from the inner ear.

It is also an object of some aspects of the present invention to provide such methods and apparatus as can be employed to deliver such compounds through the BBB to the ear using a minimally invasive approach.

It is a further object of some aspects of the present invention to provide such methods and apparatus as can facilitate delivery of large molecular weight compounds through the BBB to the ear, such as, for example, (a) pharmaceutical products having high intrinsic molecular weight, or (b) pharmaceutical products (e.g., NSAIDs) having low molecular weight, which are bound to high molecular weight compounds (e.g., albumin). In the context of the present patent application, descriptions of facilitating the movement of "large" or "high molecular weight" molecules includes compounds drawn from both (a) and (b).

It is yet a further object of some aspects of the present invention to provide cost-effective methods and apparatus for delivery of compounds through the BBB to the ear.

It is also an object of some aspects of the present invention to provide implantable apparatus which affects a property of the ear, without actually being implanted in the ear.

It is a further object of some aspects of the present invention to provide methods which affect a property of the ear without the use of implantable apparatus.

It is yet a further object of some aspects of the present invention to affect a property of the ear by using the neuroexcitatory and/or neuroinhibitory effects of odorants on nerves in the head.

These and other objects of the invention will become more apparent from the description of preferred embodiments thereof provided hereinbelow.

In some preferred embodiments of the present invention, conditions of the ear are treated by stimulating at least one "modulation target site" (MTS), as defined hereinbelow, by applying electrical, chemical, mechanical and/or odorant stimulation to the site. For some conditions, such stimulation is configured to increase permeability of the BBB, in order to enhance delivery of therapeutic molecules from the systemic blood circulation across into the ear. Alternatively or additionally, such stimulation is configured so as to increase cephalic and specifically otic blood flow, thereby increasing blood flow to various tissues of the ear and treating the condition. The electrical, chemical, mechanical and odorant stimulation techniques described herein may treat a number of ear conditions, including, but not limited to, Meniere's disease, acoustic neurinoma and neuroma, post-traumatic vertigo, vestibular neuronitis, autoimmune inner

ear disease (AIED), dizziness, and hearing loss, including sudden sensorineural hearing loss (SSHL).

In the present patent application, including the claims, a "modulation target site" (MTS) consists of:

- an otic ganglion;
- an afferent fiber going into the otic ganglion;
- an efferent fiber going out of the otic ganglion;
- a sphenopalatine ganglion (SPG) (also called a pterygopalatine ganglion);
- an anterior ethmoidal nerve;
- a posterior ethmoidal nerve;
- a communicating branch between the anterior ethmoidal nerve and the SPG (retro-orbital branch);
- a communicating branch between the posterior ethmoidal nerve and the SPG (retro-orbital branch)
- a nerve of the pterygoid canal (also called a vidian nerve), such as a greater superficial petrosal nerve (a preganglionic parasympathetic nerve) or a lesser deep petrosal nerve (a postganglionic sympathetic nerve);
- a greater palatine nerve;
- a lesser palatine nerve;
- a sphenopalatine nerve;
- a communicating branch between the maxillary nerve and the sphenopalatine ganglion;
- a nasopalatine nerve;
- a posterior nasal nerve; or
- an infraorbital nerve.

In some preferred embodiments of the present invention, the electrical, chemical, mechanical and/or odorant stimulation techniques described herein enhance delivery of therapeutic molecules across the BBB by modulation of at least one MTS and/or another parasympathetic center. These techniques typically stimulate the nerve fibers of the MTS, thereby inducing the middle and anterior cerebral arteries to dilate, and also causing the walls of these cerebral arteries to become more permeable to large molecules. In this manner, the movement of large pharmaceutical molecules from within blood vessels to tissue of the ear, is substantially increased. Without the use of the techniques described herein, the intact BBB generally has a limiting effect on the passage of these compounds to the region of the ear.

It is to be appreciated that references herein to specific modulation target sites are to be understood as including other modulation target sites, as appropriate.

It is further to be appreciated that implantation and modulation sites, methods of implantation, and parameters of modulation are described herein by way of illustration and not limitation, and that the scope of the present invention includes other possibilities which would be obvious to someone of ordinary skill in the art who has read the present patent application.

It is yet further to be appreciated that while some preferred embodiments of the invention are generally described herein with respect to electrical transmission of power and electrical modulation of tissue, other modes of energy transport may be used as well. Such energy includes, but is not limited to, direct or induced electromagnetic energy, radiofrequency (RF) transmission, mechanical vibration, ultrasonic transmission, optical power, and low power laser energy (via, for example, a fiber optic cable).

It is additionally to be appreciated that whereas some preferred embodiments of the present invention are described with respect to application of electrical currents to tissue, this is to be understood in the context of the present patent application and in the claims as being substantially equivalent to applying an electrical field, e.g., by creating a voltage drop between two electrodes.

In some preferred embodiments of the present invention, stimulation of at least one MTS is achieved by presenting odorants to an air passage of a patient, such as a nasal cavity or the throat, so as to treat an ear condition. The temporal profile and other quantitative characteristics of such odorant modulation are believed by the present

inventors to have a mechanism of action that has a neuroanatomical basis overlapping with that of the electrical modulation of the otic ganglion, the SPG or another MTS. Furthermore, experimental animal evidence collected by the inventors and described in US Provisional Patent Application 60/368,657 to Shalev and Gross entitled, "SPG stimulation," filed March 28, 2002, which is assigned to the assignee of the present invention and is incorporated herein by reference, suggest a correlation between the mechanisms of increasing cerebral blood flow and increased cerebrovascular permeability. For some applications, odorant-presentation techniques for treating an ear condition described herein are practiced in combination with techniques described in US Provisional Patent Application 60/376,048, filed April 25, 2002, entitled, "Methods and apparatus for modifying properties of the BBB and cerebral circulation by using the neuroexcitatory and/or neuroinhibitory effects of odorants on nerves in the head," which is assigned to the assignee of the present patent application and is incorporated herein by reference.

Odorants that may increase or decrease cerebral blood flow and/or the permeability of the BBB, and which are suitable for treating an ear condition, include, but are not limited to, propionic acid, cyclohexanone, amyl acetate, acetic acid, citric acid, carbon dioxide, sodium chloride, ammonia, menthol, alcohol, nicotine, piperine, gingerol, zingerone, allyl isothiocyanate, cinnamaldehyde, cuminaldehyde, 2-propenyl/2-phenylethyl isothiocyanate, thymol, and eucalyptol.

The odorants reach the appropriate neural structures and induce vasodilatation, vasoconstriction and/or cerebrovascular permeability changes. Delivery of a drug to the ear via the brain can be achieved by mixing the drug with the odorant; by intravenously, intraperitoneally, or intramuscularly administering the drug while the odorant is having an effect, or therebefore; or by other delivery methods known in the art.

In some preferred embodiments of the present invention, stimulation of at least one MTS is achieved by applying a neuroexcitatory agent to the MTS. Suitable neuroexcitatory agents include, but are not limited to acetylcholine and urecholine. For some applications, the MTS is stimulated by applying a neuroinhibitory agent, such as atropine, hexamethonium, or a local anesthetic (e.g., lidocaine).

In some preferred embodiments of the present invention, stimulation of the MTS is achieved by applying mechanical stimulation to the MTS, e.g., vibration.

As described above, it is believed that substantially all pharmacological treatments aimed at structures of the ear are amenable for use in combination with techniques described herein, including electrical, odorant, chemical and mechanical techniques for stimulating at least one MTS.

There is therefore provided, in accordance with an embodiment of the present invention, apparatus for treating a condition of an ear of a subject, including a stimulator adapted to stimulate at least one site of the subject at a level sufficient to treat the ear condition, the site selected from the list consisting of: an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, a sphenopalatine ganglion (SPG) of the subject, an anterior ethmoidal nerve of the subject, a posterior ethmoidal nerve of the subject, a communicating branch between an anterior ethmoidal nerve and a retro-orbital branch of an SPG of the subject, a communicating branch between a posterior ethmoidal nerve and a retro-orbital branch of an SPG of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, a nasopalatine nerve of the subject, a posterior nasal nerve of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject.

In an embodiment, the condition includes one or more of the following:

- Meniere's disease;
- acoustic neurinoma;
- acoustic neuroma;
- post-traumatic vertigo;
- vestibular neuronitis;
- autoimmune inner ear disease (AIED);
- hearing loss;
- ototoxicity; and
- a tumor of the ear,

and the apparatus is adapted to treat the condition.

In an embodiment, the site includes one or more of the following:

- the otic ganglion of the subject;
- the afferent fiber going into the otic ganglion of the subject;
- the efferent fiber going out of the otic ganglion of the subject;
- the SPG of the subject;
- the anterior ethmoidal nerve of the subject;
- the posterior ethmoidal nerve of the subject;
- the communicating branch between the anterior ethmoidal nerve and the retro-orbital branch of the SPG of the subject;
- the communicating branch between the posterior ethmoidal nerve and the retro-orbital branch of the SPG of the subject;
- the greater palatine nerve of the subject;
- the lesser palatine nerve of the subject;
- the sphenopalatine nerve of the subject;
- the communicating branch between the maxillary nerve and the SPG of the subject;
- the nasopalatine nerve of the subject;
- the posterior nasal nerve of the subject;
- the infraorbital nerve of the subject;
- the vidian nerve of the subject;
- the greater superficial petrosal nerve of the subject; and
- the lesser deep petrosal nerve of the subject,

and the stimulator is adapted to stimulate the site.

In an embodiment, the stimulator is adapted to configure the stimulation of the site to induce an increase in cephalic blood flow of the subject sufficient to treat the ear

condition. In an embodiment, the stimulator is adapted to configure the stimulation of the site to induce an increase in otic blood flow of the subject sufficient to treat the ear condition.

In an embodiment, the stimulator is adapted to configure the stimulation of the site to induce an increase in vasomotor control over blood vessels associated with a vestibulocochlear nerve of the subject sufficient to increase clearance, from an inner ear of the ear, of at least one constituent accumulated in the inner ear, the at least one constituent selected from the list consisting of: a metabolite and fluid.

In an embodiment, the condition includes dizziness, and the apparatus is adapted to treat the dizziness. For some applications, the stimulator is adapted to configure the stimulation of the site to increase blood flow to structures of an inner ear of the ear to a level sufficient to treat the dizziness.

In an embodiment, the condition includes sudden sensorineural hearing loss (SSHL), and the apparatus is adapted to treat the SSHL. For some applications, the stimulator is adapted to configure the stimulation of the site to increase blood flow to structures of an inner ear of the ear to a level sufficient to treat the SSHL.

In an embodiment, the condition includes inner-ear ischemia, and the apparatus is adapted to treat the inner-ear ischemia. For some applications, the stimulator is adapted to configure the stimulation of the site to induce an increase in blood flow in a region of an inner ear of the ear to a level sufficient to treat the inner-ear ischemia.

In an embodiment, the stimulator is adapted to configure the stimulation of the site to induce an increase in molecular passage across a blood brain barrier (BBB) of the subject. For some applications, the stimulator is adapted to configure the stimulation of the site to increase the molecular passage across the BBB to a magnitude that increases passage of a therapeutic agent from a systemic blood circulation of the subject through the BBB into a vicinity of the ear of the subject, so as to treat the ear condition.

For some applications, the therapeutic agent is selected from the list consisting of: a chemotherapeutic agent, a diuretic, an anti-inflammatory drug, an anti-viral drug, an anti-bacterial drug, a transtympanic agent, and an anti-Tumor Necrosis Factor compound, and the stimulator is adapted to configure the stimulation of the site to increase the

molecular passage across the BBB to the magnitude that increases passage of the selected therapeutic agent.

For some applications, the stimulator is adapted to configure the stimulation of the site to increase the molecular passage across the BBB to a magnitude that increases passage of the therapeutic agent from the systemic blood circulation through the BBB into a vicinity of a vestibulocochlear nerve of the subject.

For some applications, the therapeutic agent includes a neurotrophic factor, and the stimulator is adapted to configure the stimulation of the site to increase the molecular passage across the BBB to a magnitude that increases passage of the neurotrophic factor. For some applications, the neurotrophic factor is selected from the list consisting of: GDNF, BDNF, NT3, NT4/5, Ig NGF, IL-6, LIF, CNTF, OSM, CNTF, LIF, IGF-1, IGF-2, TGF-alpha, TGF-beta 1, TGF-beta 2, TGF-beta 3, NTN, PSP, PDGF, SCF, CNTF, and IGF2, and the stimulator is adapted to configure the stimulation of the site to increase the molecular passage across the BBB to a magnitude that increases passage of the selected neurotrophic factor.

In an embodiment, the stimulator includes an electrical stimulator, adapted to drive a current into the site, so as to stimulate the site. For some applications, the electrical stimulator is adapted to be implanted in a body of the subject.

In an embodiment, the electrical stimulator includes: at least one electrode, adapted to be placed in a vicinity of the site; and a control unit, adapted to drive the electrode to apply the current to the site. For some applications, the electrode is adapted to be implanted in the vicinity of the site. For some applications, the site includes a first site and a second site, at least 2 mm from the first site, and the at least one electrode includes a first electrode and a second electrode, the first electrode adapted to be placed in a vicinity of the first site, and the second electrode adapted to be placed in a vicinity of the second site.

In an embodiment, the stimulator includes a chemical stimulator device, adapted to apply a neuroexcitatory agent to the site at a dosage sufficient to stimulate the site. For some applications, the neuroexcitatory agent includes acetylcholine, and the chemical stimulator device is adapted to apply the acetylcholine. For some applications, the neuroexcitatory agent includes an acetylcholine-like molecule, and the chemical stimulator device is adapted to apply the acetylcholine-like molecule. For some

applications, the neuroexcitatory agent includes urecholine, and the chemical stimulator device is adapted to apply the urecholine.

In an embodiment, the stimulator includes a mechanical stimulator device, adapted to apply mechanical stimulation to the site. For some applications, the mechanical stimulator device is adapted to apply vibration to the site.

There is also provided, in accordance with an embodiment of the present invention, a method for treating a condition of an ear of a subject, including stimulating at least one site of the subject, so as to treat the ear condition, the site selected from the list consisting of: an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, a sphenopalatine ganglion (SPG) of the subject, an anterior ethmoidal nerve of the subject, a posterior ethmoidal nerve of the subject, a communicating branch between an anterior ethmoidal nerve and a retro-orbital branch of an SPG of the subject, a communicating branch between a posterior ethmoidal nerve and a retro-orbital branch of an SPG of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, a nasopalatine nerve of the subject, a posterior nasal nerve of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject.

The present invention will be more fully understood from the following detailed description of the preferred embodiments thereof, taken together with the drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A and 1B are schematic pictorial views of a fully implantable stimulator for stimulation of an MTS, in accordance with a preferred embodiments of the present invention;

Fig. 2 is a schematic pictorial view of another stimulator for stimulation of an MTS, in accordance with a preferred embodiment of the present invention;

Fig. 3 is a schematic block diagram illustrating circuitry for use with the stimulator shown in Fig. 1, in accordance with a preferred embodiment of the present invention;

Fig. 4 is a schematic block diagram illustrating circuitry for use with the stimulator shown in Fig. 2, in accordance with a preferred embodiment of the present invention;

Figs. 5A and 5B are schematic illustrations depicting different modes of operation of stimulators such as those shown in Figs. 1 and 2, in accordance with preferred embodiments of the present invention;

Fig. 6 is a schematic illustration of a mode of operation of the stimulators shown in Figs. 1 and 2, synchronized with a drug delivery system, in accordance with a preferred embodiment of the present invention;

Fig. 7 is a schematic block diagram illustrating circuitry for use with the stimulator shown in Fig. 1, where the stimulator is driven by an external controller and energy source using a modulator and a demodulator, in accordance with a preferred embodiment of the present invention;

Fig. 8 depicts sample modulator and demodulator functions for use with the circuitry of Fig. 7, in accordance with a preferred embodiment of the present invention;

Figs. 9, 10A, and 10B are schematic diagrams illustrating further circuitry for use with implantable stimulators, in accordance with respective preferred embodiments of the present invention;

Figs. 11 and 12 are bar graphs showing experimental data collected in accordance with a preferred embodiment of the present invention;

Fig. 13 is a schematic illustration of a sensor for application to a blood vessel, in accordance with a preferred embodiment of the present invention; and

Fig. 14 is a schematic sectional illustration of a nasal inhaler, for use in presenting an odorant to a subject, in accordance with a preferred embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Figs. 1A and 1B are schematic pictorial views of a fully-implantable stimulator 4, for stimulation of a "modulation target site" (MTS), as defined hereinbelow, such as a sphenopalatine ganglion (SPG) 6 (Fig. 1A) or an otic ganglion 9 (Fig. 1B), in accordance with a preferred embodiments of the present invention. In Fig. 1A, a human nasal cavity 2 is shown, and stimulator 4 is implanted between the hard palate and the

mucoperiosteum (not shown) of the roof of the mouth. In Fig. 1B, stimulator 4 is also implanted between the hard palate and the mucoperiosteum (not shown) of the roof of the mouth. Branches of parasympathetic neurons coming from SPG 6 extend to the middle cerebral and anterior cerebral arteries (not shown). Preferably, one or more relatively short electrodes 7 extend from stimulator 4 to contact or to be in a vicinity of an MTS, such as SPG 6 (Fig. 1A) or otic ganglion 9 (Fig. 1B).

In the present patent application and the claims, a "modulation target site" consists of:

- an otic ganglion;
- an afferent fiber going into the otic ganglion;
- an efferent fiber going out of the otic ganglion;
- a sphenopalatine ganglion (SPG) (also called a pterygopalatine ganglion);
- an anterior ethmoidal nerve;
- a posterior ethmoidal nerve;
- a communicating branch between the anterior ethmoidal nerve and the SPG (retro orbital branch);
- a communicating branch between the posterior ethmoidal nerve and the SPG (retro orbital branch)
- a nerve of the pterygoid canal (also called a vidian nerve), such as a greater superficial petrosal nerve (a preganglionic parasympathetic nerve) or a lesser deep petrosal nerve (a postganglionic sympathetic nerve);
- a greater palatine nerve;
- a lesser palatine nerve;
- a sphenopalatine nerve;
- a communicating branch between the maxillary nerve and the sphenopalatine ganglion;

- a nasopalatine nerve;
- a posterior nasal nerve; or
- an infraorbital nerve.

For some applications, stimulator 4 is implanted on top of the bony palate, in the bottom of the nasal cavity. Alternatively or additionally, the stimulator is implanted at the lower side of the bony palate, at the top of the oral cavity. In this instance, one or more flexible electrodes 7 originating in the stimulator are passed through the palatine bone or posterior to the soft palate, so as to be in a position to stimulate the otic ganglion, the SPG or another MTS. Further alternatively or additionally, the stimulator may be directly attached to the otic ganglion, the SPG and/or to another MTS.

For some applications, stimulator 4 is delivered to a desired point within nasal cavity 2 by removably attaching stimulator 4 to the distal end of a rigid or slightly flexible introducer rod (not shown) and inserting the rod into one of the patient's nasal passages until the stimulator is properly positioned. As appropriate, the placement process may be facilitated by fluoroscopy, x-ray guidance, fine endoscopic surgery (FES) techniques or by any other effective guidance method known in the art, or by combinations of the aforementioned. Preferably, the ambient temperature and/or cerebral blood flow is measured concurrently with insertion. The cerebral blood flow may be measured with, for example, a laser Doppler unit positioned at the patient's forehead or transcranial Doppler measurements. Verification of proper implantation of the electrodes onto the appropriate neural structure may be performed by activating the device, and generally simultaneously monitoring cerebral blood flow.

The passage of certain molecules from cerebral blood vessels into the brain is hindered by the BBB. The endothelium of the capillaries, the plasma membrane of the blood vessels, and the foot processes of the astrocytes all impede uptake by the brain of the molecules. The BBB generally allows only small molecules (e.g., hydrophilic molecules of molecular weight less than about 200 Da, and lipophilic molecules of less than about 500 Da) to pass from the circulation into the brain.

As used in the present application and in the claims, the BBB comprises the tight junctions opposing the passage of most ions and large molecular weight compounds from

the blood to brain tissue, as well as from the blood to structures of the ear, such as the vestibulocochlear nerve (the eighth cranial nerve).

In accordance with a preferred embodiment of the present invention, parasympathetic activation induced by current from stimulator 4 overcomes the resistance to trans-BBB molecular movement generated by the endothelium of the cerebral capillaries and the plasma membrane. For some applications, therefore, stimulator 4 may be used to transiently remove a substantial obstacle to the passage of drugs from the blood to the ear, thereby facilitating transport of drugs to a tissue of the ear. For example, the stimulator may cyclically apply current for about two minutes, and subsequently have a rest period of between about 1 and 20 minutes.

It is hypothesized that two neurotransmitters play an important role in this change in properties of the BBB -- vasoactive intestinal polypeptide (VIP) and nitric oxide (NO). (Acetylcholine may also be involved.) VIP is a short peptide, and NO is a gaseous molecule. VIP is believed to be a major factor in facilitating plasma protein extravasation (PPE), while NO is responsible for vasodilation. For some applications, stimulator 4 is adapted to vary parameters of the current applied to an MTS, as appropriate, in order to selectively influence the activity of one or both of these neurotransmitters. For example, stimulation of the parasympathetic nerve at different frequencies can induce differential secretion -- low frequencies cause secretion of NO, while high frequencies (e.g., above about 10 Hz) cause secretion of peptides (VIP). For some applications, techniques described herein are practiced in combination with techniques described in a US patent application, filed October 2, 2003, entitled, "Targeted release of nitric oxide in the brain circulation for opening the BBB," which is assigned to the assignee of the present application and is incorporated herein by reference.

For other applications, a constant level DC signal, or a slowly varying voltage ramp is applied, in order to block parasympathetic neural activity in affected tissue. Alternatively, similar results can be obtained by stimulating at a rate higher than about 10 Hz, because this tends to exhaust neurotransmitters. Thus, stimulator 4 may be configured to induce parasympathetic electrical block, in order to cause vasoconstriction by mimicking the overall effect of chemical block on the SPG.

Fig. 2 is a schematic illustration of a stimulator control unit 8 positioned external to a patient's body, in accordance with a preferred embodiment of the present invention.

At least one flexible electrode 10 preferably extends from control unit 8, through a nostril 12 of the patient, and to a position within the nasal cavity 14 that is adjacent to SPG 6.

It is to be understood that electrodes 7 (Fig. 1A) and 10 may each comprise one or more electrodes, e.g., two electrodes, or an array of microelectrodes. For applications in which stimulator 4 comprises a metal housing that can function as an electrode, then typically one electrode 7 is used, operating in a monopolar mode. Regardless of the total number of electrodes in use, typically only a single or a double electrode extends to SPG 6 or otic ganglion 9 (Fig. 1B). Other electrodes 7 or 10 or a metal housing of stimulator 4 are preferably temporarily or permanently implanted in contact with other parts of nasal cavity 2.

Each of electrodes 7 and/or 10 preferably comprises a suitable conductive material, for example, a physiologically-acceptable material such as silver, iridium, platinum, a platinum iridium alloy, titanium, nitinol, or a nickel-chrome alloy. For some applications, one or more of the electrodes have lengths ranging from about 1 to 5 mm, and diameters ranging from about 50 to 100 microns. Each electrode is preferably insulated with a physiologically-acceptable material such as polyethylene, polyurethane, or a co-polymer of either of these. The electrodes are preferably spiral in shape, for better contact, and may have a hook shaped distal end for hooking into or near the otic ganglion 9 or the SPG. Alternatively or additionally, the electrodes may comprise simple wire electrodes, spring-loaded "crocodile" electrodes, or adhesive probes, as appropriate.

In a preferred embodiment of the invention, each one of electrodes 7 and/or 10 comprises a substantially smooth surface, except that the distal end of each such electrode is configured or treated to have a large surface area. For example, the distal tip may be porous platinized. Alternatively or additionally, at least the tip of electrode 7 or 10, and/or a metal housing of stimulator 4 includes a coating comprising an anti-inflammatory drug, such as beclomethasone sodium phosphate or beclomethasone phosphate. Alternatively, such an anti-inflammatory drug is injected or otherwise applied.

Fig. 3 is a schematic block diagram illustrating circuitry comprising an implanted unit 20 and an external unit 30, for use with stimulator 4 (Fig. 1A), in accordance with a preferred embodiment of the present invention. Implanted unit 20 preferably comprises a feedback block 22 and one or more sensing or signal application electrodes 24. Implanted unit 20 typically also comprises an electromagnetic coupler 26, which receives power

and/or sends or receives data signals to or from an electromagnetic coupler 28 in external unit 30.

External unit 30 preferably comprises a microprocessor 32 which receives an external control signal 34 (e.g., from a physician or from the patient), and a feedback signal 36 from feedback block 22. Control signal 34 may include, for example, operational parameters such as a schedule of operation, patient parameters such as the patient's weight, or signal parameters, such as desired frequencies or amplitudes of a signal to be applied to an MTS. If appropriate, control signal 34 can comprise an emergency override signal, entered by the patient or a healthcare provider to terminate stimulation or to modify it in accordance with a predetermined program. Microprocessor 32, in turn, preferably processes control signal 34 and feedback signal 36 so as to determine one or more parameters of the electric current to be applied through electrodes 24. Responsive to this determination, microprocessor 32 typically generates an electromagnetic control signal 42 that is conveyed by electromagnetic coupler 28 to electromagnetic coupler 26. Control signal 42 preferably corresponds to a desired current or voltage to be applied by electrodes 24 to an MTS, such as otic ganglion 9 or SPG 6, and, in a preferred embodiment, inductively drives the electrodes. The configuration of couplers 26 and 28 and/or other circuitry in units 20 or 30 may determine the intensity, frequency, shape, monophasic or biphasic mode, or DC offset of the signal (e.g., a series of pulses) applied to designated tissue.

Power for microprocessor 32 is typically supplied by a battery 44 or, optionally, another DC power supply. Grounding is provided by battery 44 or a separate ground 46. If appropriate, microprocessor 32 generates a display signal 38 that drives a display block 40 of external unit 30. Typically, but not necessarily, the display is activated to show feedback data generated by feedback block 22, or to provide a user interface for the external unit.

Implanted unit 20 is preferably packaged in a case made of titanium, platinum or an epoxy or other suitable biocompatible material. Should the case be made of metal, then the case may serve as a ground electrode and, therefore, stimulation typically is performed in a monopolar mode. Alternatively, should the case be made of biocompatible plastic material, two electrodes 24 are typically driven to apply current to the MTS.

For some applications, the waveform applied by one or more of electrodes 24 to designated tissue of an MTS (e.g., the otic ganglion or the SPG) comprises a waveform with an exponential decay, a ramp up or down, a square wave, a sinusoid, a saw tooth, a DC component, or any other shape known in the art to be suitable for application to tissue. Alternatively or additionally, the waveform comprises one or more bursts of short shaped or square pulses -- each pulse preferably less than about 1 ms in duration. Generally, appropriate waveforms and parameters thereof are determined during an initial test period of external unit 30 and implanted unit 20. For some applications, the waveform is dynamically updated according to measured physiological parameters, measured during a period in which unit 20 is stimulating an MTS, and/or during a non-activation (i.e., standby) period.

Fig. 4 is a schematic block diagram of circuitry for use, for example, in conjunction with control unit 8 (Fig. 2), in accordance with a preferred embodiment of the present invention. An external unit 50 comprises a microprocessor 52 supplied by a battery 54 or another DC power source. Grounding may be provided by battery 54 or by a separate ground 56. Microprocessor 52 preferably receives control and feedback signals 58 and 68 (analogous to signal 34 and 36 described hereinabove), and generates responsive thereto a stimulation signal 64 conveyed by one or more electrodes 66 to an MTS or other tissue. Typically, but not necessarily, feedback signal 68 comprises electrical feedback measured by one or more of electrodes 66 and/or feedback from other sensors on or in the patient's brain or elsewhere coupled to the patient's body. If appropriate, microprocessor 52 generates a display signal 60 which drives a display block 62 to output relevant data to the patient or the patient's physician. Typically, some or all of electrodes 66 are temporarily implanted in the patient (e.g., following a stroke), and are directly driven by wires connecting the external unit to the implanted unit.

Fig. 5A is a graph schematically illustrating a mode of operation of one or more of the devices shown in Figs. 1-4, in accordance with a preferred embodiment of the present invention. Preferably, the effect of the applied stimulation is monitored by means of a temperature transducer at an MTS (e.g., the otic ganglion or the SPG) or elsewhere in the head, e.g., in the nasal cavity. As shown in Fig. 5A for a step (ON/OFF) mode of stimulation, stimulation of an MTS or related tissue is initiated at a time T1, and this is reflected by a measurable rise in temperature (due to increased blood flow). Once the

temperature rises to a predetermined or dynamically-varying threshold (e.g., 37 °C), stimulation is terminated (time T2), responsive to which the temperature falls. As appropriate, when the temperature drops to a designated or dynamically-determined point, the stimulation is reinitiated (time T3). Preferably, suitable temperatures or other physiological parameters are determined for each patient so as to provide the optimal treatment. If appropriate, control instructions may also be received from the patient.

Fig. 5B is a graph schematically illustrating a mode of operation of one or more of the devices shown in Figs. 1-4, in accordance with another preferred embodiment of the present invention. In this embodiment, the amplitude of the waveform applied to an MTS is varied among a continuous set of values (S1), or a discrete set of values (S2), responsive to the measured temperature, in order to achieve the desired performance. It will be appreciated that other feedback parameters measured in the head (e.g., intraocular pressure, intracranial pressure and/or cerebral blood flow), as well as measured systemic parameters (e.g., heart rate) and subjective patient inputs may be used in conjunction with or separately from temperature measurements, in order to achieve generally optimal performance of the implanted apparatus.

Fig. 6 is a graph schematically illustrating a mode of operation of one or more of the devices shown in Figs. 1-4, 14, and 15, in accordance with a preferred embodiment of the present invention. In this embodiment, a drug is administered to the patient at a constant rate, e.g., intravenously, prior to the initiation of chemical, mechanical, electrical and/or odorant stimulation of an MTS at time T1. Advantageously, this prior generation of heightened concentrations of the drug in the blood tends to provide relatively rapid transfer of the drug across the BBB and into the ear, without unnecessarily prolonging the enhanced permeability of the BBB while waiting for the blood concentration of the drug to reach an appropriate level. Alternatively, for some applications it is desirable to give a single injection of a bolus of the drug shortly before or after initiation of stimulation of an MTS. Typically, combined administration and stimulation schedules are determined by the patient's physician based on the biochemical properties of each drug targeted at the ear.

Fig. 7 is a schematic block diagram showing circuitry for parasympathetic stimulation, which is particularly useful in combination with the embodiments shown in Figs. 1A and 1B, in accordance with a preferred embodiment of the present invention. An

external unit 80 preferably comprises a microprocessor 82 that is powered by a battery 84 and/or an AC power source. Microprocessor 82 is grounded through battery 84 or through an optional ground 86.

In a typical mode of operation, an external control signal 88 is input to microprocessor 82, along with a feedback signal 108 from one or more biosensors 106, which are typically disposed in a vicinity of an implanted unit 100 or elsewhere on or in the patient's body. Responsive to signals 88 and 108, microprocessor 82 preferably generates a display signal 89 which drives a display 90, as described hereinabove. In addition, microprocessor 82 preferably processes external control signal 88 and feedback signal 108, to determine parameters of an output signal 92, which is modulated by a modulator 94. The output therefrom preferably drives a current through an electromagnetic coupler 96, which inductively drives an electromagnetic coupler 98 of implanted unit 100. A demodulator 102, coupled to electromagnetic coupler 98, in turn, generates a signal 103 which drives at least one electrode 104 to apply current to an MTS or to other tissue, as appropriate.

Preferably, biosensor 106 comprises implantable or external medical apparatus including, for example, one or more of the following:

- a blood flow sensor,
- a temperature sensor,
- a chemical sensor,
- an ultrasound sensor,
- transcranial Doppler (TCD) apparatus,
- laser-Doppler apparatus,
- a systemic or intracranial blood pressure sensor (e.g., comprising a piezoelectric crystal or capacitive sensor fixed to a major cerebral blood vessel, capable of detecting a sudden blood pressure increase indicative of a clot),
- a tissue vitality sensor, e.g., comprising laser Doppler or other optical apparatus for detecting a NAD/NADH ratio in tissue, using optical techniques known in the art for detecting the metabolic state of a tissue,

- a kinetics sensor, comprising, for example, an acceleration, velocity, or level sensor (e.g., a mercury switch), for indicating body dispositions such as a sudden change in body attitude (as in collapsing),
- an electroencephalographic (EEG) sensor comprising EEG electrodes attached to, or implanted in, the patients head, for indicating changes in neurological patterns, such as symptoms of stroke,
- a blood vessel clot detector (e.g., as described hereinbelow with reference to Fig. 13), or
- other monitors of physiological quantities suitable for carrying out the objects of this or other embodiments of the present invention.

Fig. 8 is a schematic illustration showing operational modes of modulator 94 and/or demodulator 102, in accordance with a preferred embodiment of the present invention. The amplitude and frequency of signal 92 in Fig. 7 can have certain values, as represented in the left graph; however, the amplitude and frequency are modulated so that signal 103 has different characteristics.

Fig. 9 is a schematic illustration of further apparatus for stimulation of an MTS, in accordance with a preferred embodiment of the present invention. In this embodiment, substantially all of the processing and signal generation is performed by circuitry in an implanted unit 110 in the patient, and, preferably, communication with a controller 122 in an external unit 111 is performed only intermittently. The implanted unit 110 preferably comprises a microprocessor 112 coupled to a battery 114. Microprocessor 112 generates a signal 116 that travels along at least one electrode 118 to stimulate the MTS. A feedback signal 120 from a biosensor (not shown) and/or from electrode 118 is received by microprocessor 112, which is adapted to modify stimulation parameters responsive thereto. Preferably, microprocessor 112 and controller 122 are operative to communicate via wireless couplers 126 and 124 (e.g., electromagnetic couplers), in order to exchange data or to change parameters. Further preferably, battery 114 is wirelessly rechargeable (e.g., inductively rechargeable by electromagnetic coupling).

Fig. 10A is a schematic illustration of a stimulator 150, in accordance with a preferred embodiment of the present invention. Preferably, substantially all of the electronic components (including an electronic circuit 158 having a rechargeable energy

source) are encapsulated in a biocompatible metal case 154. An inductive coil 156 and at least one electrode 162 are preferably coupled to circuit 158 by means of a feed-through coupling 160. The inductive coil is preferably isolated by an epoxy coating 152, which allows for higher efficiency of the electromagnetic coupling.

Fig. 10B is a schematic illustration of another configuration of an implantable stimulator, in accordance with a preferred embodiment of the present invention. Preferably, substantially all of the electronic components (including an inductive coil 176 and an electronic circuit 178 having a rechargeable energy source) are encapsulated in a biocompatible metal case 174. One or more feed-throughs are preferably provided to enable coupling between at least one electrode 182 and the electronic circuit, as well as between inductive coil 176 and another inductive coil (not shown) in communication therewith.

With reference to Figs. 10A and 10B, the energy source for electronic circuits 158 and 178 may comprise, for example, a primary battery, a rechargeable battery, or a super capacitor. For applications in which a rechargeable battery or a super capacitor is used, any kind of energizing means may be used to charge the energy source, such as (but not limited to) standard means for inductive charging or a miniature electromechanical energy converter that converts the kinetics of the patient movement into electrical charge. Alternatively, an external light source (e.g., a simple LED, a laser diode, or any other light source) may be directed at a photovoltaic cell in the electronic circuit. Further alternatively, ultrasound energy is directed onto the implanted unit, and transduced to drive battery charging means.

Figs. 11 and 12 are bar graphs showing experimental results obtained during rat experiments performed in accordance with a preferred embodiment of the present invention. A common technique in monitoring bio-distribution of materials in a system includes monitoring the presence and level of radio-labeled tracers. These tracers are unstable isotopes of common elements (e.g., Tc, In, Cr, Ga, and Gd), conjugated to target materials. The chemical properties of the tracer are used as a predictor for the behavior of other materials with similar physiochemical properties, and are selected based on the particular biological mechanisms that are being evaluated. Typically, a patient or experimental animal is placed on a Gamma camera, or target tissue samples can be harvested and placed separately into a well counter. For the purpose of the present set of

experiments which were performed, the well counter method was chosen due to its higher sensitivity and spatial resolution. A series of experiments using 99Tc-DTPA (DTPA molecule conjugated to a 99-Technetium isotope) were performed. The molecular weight of 99Tc-DTPA is 458 Da, its lipophilicity is negative, and its electric charge is +1. These parameters are quite similar with pharmacological agents used in standard chemotherapy, such as tamoxifen, etoposide and irinotecan.

Figs. 11 and 12 show results obtained using 99Tc-DTPA penetration assays using ordinary brain sampling techniques (Fig. 11) and peeled brain techniques (Fig. 12). The x-axis of each graph represents different experimental runs, and the y-axis of each graph is defined as: [(hemisphere radioactivity) / (hemisphere weight)] / [(total injected radioactivity) / (total animal weight)]. The results obtained demonstrate an average 2.5-fold increase in the penetration of 99Tc-DTPA to the rat brain. It is noted that these results were obtained by unilateral stimulation of the SPG. The inventors believe that bilateral SPG stimulation will approximately double drug penetration, relative to unilateral SPG stimulation.

In both Fig. 11 and Fig. 12, some animals were designated as control animals, and other animals were designated as test animals. In each group, the left and right hemispheres were tested separately, and the height of each bar represents, for a given animal and a given hemisphere, the normalized level of radioactivity as defined above. Thus, Fig. 11 shows results from a total of four test hemispheres and four control hemispheres. Fig. 12 shows results from six test hemispheres and fourteen control hemispheres. The juxtaposition of control and test bars in the bar graphs is not meant to imply pairing of control and test hemispheres.

Fig. 13 is a schematic illustration of acoustic or optical clot detection apparatus 202, for use, for example, in providing feedback to any of the microprocessors or other circuitry described hereinabove, in accordance with a preferred embodiment of the present invention. The detection is preferably performed by coupling to a major blood vessel 200 (e.g., the internal carotid artery or aorta) a detecting element comprising an acoustic or optical transmitter/receiver 206, and an optional reflecting surface 204. Natural physiological liquids may serve as a mediating fluid between the device and the vessel. Preferably, the transmitter/receiver generates an ultrasound signal or electromagnetic signal which is reflected and returned, and a processor evaluates changes in the returned

signal to detect indications of a newly-present clot. Alternatively, a transmitter is placed on side of the vessel and a receiver is placed on the other side of the vessel. In either case, for some applications, more than one such apparatus 202 are placed on the vessel, in order to improve the probability of successful clot detection for possible estimation of the clot's direction of motion within the vessel, and to lower the false alarm (i.e. false detection) rate.

Embodiments of the present invention have many medical applications for treating conditions of the ear. For example, therapeutic agents can be administered to tissue of the ear in order to treat a condition of the ear. Many drugs, including, but not limited to, chemotherapeutic agents, anti-inflammatory, anti-viral, and anti-bacterial drugs, have limited transport through the blood-brain barrier (BBB), either due to their high molecular weight, hydrophilicity, or high plasma binding.

In a preferred embodiment of the present invention, an odorant is presented to an air passage of a patient, such as a nasal cavity or the throat, so as to increase otic and cephalic blood flow, in order to treat a condition of the ear. Alternatively or additionally, an odorant is similarly presented in order to enhance delivery of therapeutic molecules across the BBB and to the ear, in order to treat a condition of the ear.

Fig. 14 is a schematic sectional illustration of a nasal inhaler 300, for use in presenting an odorant to a subject, in accordance with a preferred embodiment of the present invention. Nasal inhaler 300 preferably comprises apparatus known in the art, such as an aqueous spray nasal inhaler, a metered dose nasal inhaler, or an air-dilution olfactometer. The odorant is stored in an odorant-storage vessel 302, and is delivered to a nasal passage using an odorant-delivery element 304, such as a nasal piece. Alternatively or additionally, the odorant is presented by means of an orally-dissolvable capsule that releases the active odorants upon contact with salivary liquids. The odorants reach the appropriate neural structures and induce vasodilatation, vasoconstriction and/or cerebrovascular permeability changes.

In a preferred embodiment of the present invention, stimulation of the MTS is achieved by applying a neuroexcitatory agent to the MTS. Suitable neuroexcitatory agents include, but are not limited to acetylcholine and urecholine. For some applications, the MTS is stimulated by applying a neuroinhibitory agent, such as atropine, hexamethonium, or a local anesthetic (e.g., lidocaine).

In a preferred embodiment of the present invention, stimulation of the MTS is achieved by applying mechanical stimulation to the MTS, e.g., vibration.

In a preferred embodiment of the present invention, techniques of electrical, chemical, mechanical and/or odorant stimulation are used to treat a condition of the ear. For some conditions, such stimulation is configured so as to increase otic and cephalic blood flow, thereby increasing blood flow to various tissues of the ear and into the region of the ear, so as to treat tumors and other conditions. Alternatively or additionally, such stimulation is configured to increase permeability of the BBB, in order to enhance delivery of therapeutic molecules across the BBB and into the ear, so as to treat tumors and other conditions of the ear.

In a preferred embodiment of the present invention, conditions of the ear are treated by applying bipolar stimulation, in which a first electrode is applied to a first MTS, and a second electrode is applied to a second MTS.

These stimulation techniques, alone or in combination, are believed to be particularly useful for treating the following ear conditions. It is to be noted that, in the disclosure that follows, any descriptions of possible therapeutic mechanisms are by way of illustration only, and the scope of the present invention includes treatments that result from other mechanisms as well.

Meniere's disease (endolymphatic hydrops)

Stimulation techniques described herein are used to treat Meniere's disease (endolymphatic hydrops) by increasing the permeability of the BBB to pharmaceutical agents, such as antibiotic (antiviral or antibacterial), diuretic, anti-inflammatory, and/or transtympanic (e.g., Corticosteroid, Gentamicin, Streptomycin) agents. Alternatively or additionally, stimulation of an MTS is utilized to exercise vasomotor control over blood vessels associated with the vestibulocochlear nerve, thereby improving the metabolic state of the neural tissue and increasing the clearance of damaging metabolites and fluid (e.g. endolymphatic fluid) that have accumulated in the inner ear.

Acoustic neurinoma and neuroma (acoustic schwannoma)

Stimulation techniques described herein are used to treat acoustic neurinoma and acoustic neuroma. It is hypothesized that the vestibulocochlear nerve (the eighth cranial nerve) is at least partially protected by the BBB. Therefore, increasing the permeability of

the BBB in the vicinity of the vestibulocochlear nerve to pharmaceutical agents aids in the management of these conditions. Further, stimulation of an MTS exercises vasomotor control over blood vessels associated with the vestibulocochlear nerve, thereby helping maintain the vitality of the neural tissue during and after the exposure to cytotoxic compounds that may be administered for treating the acoustic neurinoma or neuroma.

Post-traumatic vertigo (inner ear concussion)

Stimulation techniques described herein are used to treat post-traumatic vertigo (inner ear concussion) by increasing the permeability of the BBB, thereby (a) facilitating the effective delivery to the inner ear of pharmaceutical agents, such as anti-inflammatory drugs (e.g., NSAIDs or corticosteroids), diuretics (e.g., corticosteroids), and transtympanic medications; (b) increasing clearance of excessive fluid and of toxic metabolites from the region of the inner ear; and/or (c) increasing cephalic blood flow so as to improve the metabolic state of the tissue by increased supply of oxygen and other nutrients to the metabolically-compromised region.

Vestibular neuronitis (acute labyrinthitis)

Stimulation techniques described herein are used to treat vestibular neuronitis (acute labyrinthitis) by increasing the permeability of the BBB to pharmaceutical agents, such as antibiotic (antiviral or antibacterial), diuretic, and/or anti-inflammatory agents. Alternatively or additionally, stimulation of an MTS exercises vasomotor control over blood vessels associated with the vestibulocochlear nerve, thereby improving the metabolic state of the neural tissue and increasing the clearance of damaging metabolites and fluid (e.g. endolymphatic fluid) that have accumulated in the inner ear.

Autoimmune inner ear disease (AIED)

Stimulation techniques described herein are used to treat AIED by increasing the permeability of the BBB to pharmaceutical agents, such as antibiotic (antiviral or antibacterial) agents, diuretic agents, anti-inflammatory drugs, chemotherapeutic (e.g., Cytoxan or Methotrexate) agents, and anti-Tumor Necrosis Factor compounds (e.g., Enbrel®), thereby increasing the efficacy of drug delivery into the region of the inner ear. Alternatively or additionally, stimulation of an MTS exercises vasomotor control over blood vessels associated with the vestibulocochlear nerve, thereby improving the

metabolic state of the neural tissue and increasing the clearance of damaging metabolites and fluid (e.g. endolymphatic fluid) that have accumulated in the inner ear.

Dizziness

Stimulation techniques described herein are used to treat dizziness by increasing the permeability of the BBB, thereby (a) facilitating the effective delivery to the inner ear of pharmaceutical agents, such as anti-inflammatory drugs (e.g., NSAIDs), and/or (b) increasing blood flow to structures of the inner ear when regional circulation is compromised.

Sudden sensorineural hearing loss (SSHL)

Stimulation techniques described herein are used to treat SSHL by increasing the permeability of the BBB, thereby (a) facilitating the effective delivery to the inner ear of pharmaceutical agents, such as anti-inflammatory drugs (e.g., NSAIDs or steroids), and/or (b) increasing blood flow to structures of the inner ear when regional circulation is compromised, and/or as an adjuvant therapy for carbogen inhalation. Anti-inflammatory drugs are beneficial in reducing inflammatory processes. In addition, administration of steroids in combination with the techniques described herein is helpful for conditions in which the autoimmune system is involved.

Hearing loss – restorative treatment using neurotrophic factors

Stimulation techniques described herein are used to treat ototoxicity by increasing the permeability of the BBB, thereby facilitating the effective delivery of various neurotrophic factors. Such ototoxicity may be caused by the administration of pharmaceutical agents, such as antibiotics (e.g., aminoglycoside) and antineoplastic agents (e.g., platinum-based chemotherapy such as cisplatin), or by radiation therapy. Additionally, stimulation techniques described herein are used to treat inherited sensorineural degeneration for noise trauma, and in general for idiopathic hearing loss, by increasing the permeability of the BBB, thereby facilitating the effective delivery of various neurotrophic factors. Suitable neurotrophic factors include, but are not limited to, GDNF, BDNF, NT3, NT4/5, Ig NGF, IL-6, LIF, CNTF, OSM, CNTF, LIF, IGF-1, IGF-2, TGF-alpha, TGF-beta 1, TGF-beta 2, TGF-beta 3, NTN, PSP, PDGF, SCF, CNTF and IGF2. For some applications, the administration of such compounds is performed in conjunction with techniques described in the above-cited US Patent 5,929,041 to Magal.

In an embodiment, neurotrophic factors are administered directly into the systemic blood circulation in conjunction with increasing the permeability of the BBB. Alternatively or additionally, neurotrophic factors are produced locally at the target site following systemic administration of genes that code for such factors, together with stimulation of an MTS to increase the permeability of the BBB. Further alternatively or additionally, neurotrophic factors are delivered into the inner ear via viral vectors that carry the gene that codes for these trophic factors.

In an embodiment, stimulation techniques described herein are used to manage inner-ear ischemia by increasing blood flow in the region of the inner ear.

In some embodiments of the present invention, techniques described herein are practiced in combination with techniques described in one or more of the following co-assigned patent applications: (i) US Provisional Patent Application 60/426,180, filed November 14, 2002, entitled, "Surgical tools and techniques for stimulation," or a PCT patent application of the same name claiming priority therefrom, filed on even date with the present patent application, (ii) US Provisional Patent Application 60/426,182, filed November 14, 2002, entitled, "Stimulation circuitry and control of electronic medical device," and (iii) US Patent Application 10/294,310, filed November 14, 2002, entitled, "Stimulation for treating eye pathologies," which published as US Patent Application Publication 2003/0176898. All of these applications are incorporated herein by reference. Alternatively or additionally, techniques described herein are practiced in combination with techniques described in one or more of the references cited in the Background section hereinabove.

Techniques described in this application may be practiced in combination with methods and apparatus described in one or more of the following patent applications, which are assigned to the assignee of the present patent application and are incorporated herein by reference:

- US Patent Application 10/258,714, filed October 25, 2002, entitled, "Method and apparatus for stimulating the sphenopalatine ganglion to modify properties of the BBB and cerebral blood flow," or the above-referenced PCT Publication WO 01/85094
- US Provisional Patent Application 60/364,451, filed March 15, 2002, entitled, "Applications of stimulating the sphenopalatine ganglion (SPG)"

- US Provisional Patent Application 60/368,657, filed March 28, 2002, entitled, "SPG Stimulation"
- US Provisional Patent Application 60/388,931, filed June 14, 2002, entitled "Methods and systems for management of Alzheimer's disease"
- US Provisional Patent Application 60/400,167, filed July 31, 2002, entitled, "Delivering compounds to the brain by modifying properties of the BBB and cerebral circulation"
- US Patent Application US 10/294,343, filed November 14, 2002, entitled, "Administration of anti-inflammatory drugs into the CNS"
- US Provisional Patent Application 60/426,181, filed November 14, 2002, entitled, "Stimulation for treating ear pathologies"
- US Provisional Patent Application 60/448,807, filed February 20, 2003, entitled, "Stimulation for treating autoimmune-related disorders of the CNS"
- US Provisional Patent Application 60/461,232 to Gross et al., filed April 8, 2003, entitled, "Treating abnormal conditions of the mind and body by modifying properties of the blood-brain barrier and cephalic blood flow"
- PCT Patent Application PCT / IL03 / 00338 to Shalev, filed April 25, 2003, entitled, "Methods and apparatus for modifying properties of the BBB and cerebral circulation by using the neuroexcitatory and/or neuroinhibitory effects of odorants on nerves in the head"
- a US provisional patent application, filed September 26, 2003, entitled, "Diagnostic applications of stimulation"
- a US patent application, filed October 2, 2003, entitled, "Targeted release of nitric oxide in the brain circulation for opening the BBB"
- a PCT patent application, filed on even date herewith, entitled, "Surgical tools and techniques for stimulation"

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and subcombinations of the various

features described hereinabove, as well as variations and modifications thereof that are not in the prior art, which would occur to persons skilled in the art upon reading the foregoing description. For example, elements which are shown in a figure to be housed within one integral unit may, for some applications, be disposed in a plurality of distinct units. Similarly, apparatus for communication and power transmission which are shown to be coupled in a wireless fashion may be, alternatively, coupled in a wired fashion, and apparatus for communication and power transmission which are shown to be coupled in a wired fashion may be, alternatively, coupled in a wireless fashion.